ACUTE TOXICITY SUMMARY

METHANOL

(methyl alcohol, wood spirit, carbinol, wood alcohol, wood naphtha)

CAS Registry Number: 67-56-1

I. Acute Toxicity Summary (for a 1-hr exposure)

Inhalation reference exposure level	**28,000 µg/m³**
Critical effect(s)	subtle impairment in the performance of complicated tasks
Hazard Index target(s)	Nervous System

II. Physical and Chemical Properties (HSDB, 1993 except as noted)

Description	colorless liquid
Molecular formula	CH_3OH
Molecular weight	32.04
Density	0.7915 g/cm^3 @ 20°C
Boiling point	64.5°C
Melting point	-97.8°C
Vapor pressure	92 mm Hg @ 20°C
Flashpoint	12°C, closed cup
Explosive limits	lower = 7.3% upper = 36%
Solubility	methanol is miscible with water, ethanol, ether and many other organic solvents
Odor threshold	160 ppm (geometric mean) (AIHA, 1989)
Odor description	sour/sweet (AIHA, 1989)
Metabolites	metabolized to formaldehyde, then formate
Conversion factor	1 ppm = 1.31 mg/m³ @ 25°C

III. Major Uses and Sources

Originally distilled from wood, methanol is now manufactured synthetically from carbon oxides and hydrogen. Methanol is primarily used for the manufacture of other chemicals and as a solvent. It is also added to a variety of commercial and consumer products such as windshield washing fluid and de-icing solution, duplicating fluids, solid canned fuels, paint remover, model airplane fuels, embalming fluids, lacquers, inks and as alternative motor fuel. Methanol is released in large quantities from pulp and paper mills.

IV. Acute Toxicity to Humans

Methanol is easily absorbed following ingestion, inhalation, or dermal exposure and is metabolized by the liver to formaldehyde, then formate. The latter metabolite is responsible for the metabolic acidosis and ocular effects characteristic of acute methanol poisoning. Odor and irritation are not adequate warnings of overexposure to methanol (Reprotext, 1999).

Upon ingestion or inhalation, methanol initially has a narcotic effect followed by an asymptomatic period of approximately 10 to 15 hours (Rowe and McCollister, 1978). After this period, methanol may produce nausea, vomiting, dizziness, headaches, vertigo, respiratory difficulty, lethargy, abdominal pain, pain in the extremities, visual disturbances, and metabolic acidosis (ATSDR, 1993; NIOSH, 1976). The visual disturbances vary from spots or cloudiness of vision to complete blindness (Grant, 1986). Methanol toxicity can result in coma and death by respiratory or cardiac arrest.

In one study, symptoms of blurred vision, headaches, dizziness, nausea, and skin problems were reported in teachers' aides who were exposed to duplicating fluid containing 99% methanol while working with "spirit duplicators" (Frederick *et al*., 1984). A dose-response relationship was observed between the amount of time spent at the duplicator and the incidence of symptoms. The concentrations of methanol in the breathing zones near the machines in 12 schools ranged from 485 to 4,096 mg/m^3 (365 to 3,080 ppm) for a 15 minute sample.

Employees working in the proximity of direct process duplicating machines complained of frequent headaches and dizziness (Kingsley and Hirsch, 1954). Air concentrations of methanol ranged from 15 ppm (20 mg/m^3) to 375 ppm (490 mg/m^3).

In a pilot study, 12 young, paid, male volunteers were exposed to filtered air and to 250 mg/m^3 (192 ppm) methanol vapor for 75 minutes and were administered a battery of 20 neurobehavioral and neurophysiological tests before, during, and after exposure (Cook *et al*., 1991). Methanol had no significant effect on the subjects' performance for all but two of the tests. Although statistically significant effects were observed in one test measuring fatigue and concentration (fatigue scale score, $p = 0.02$) and a trend was observed in a test measuring the latency of visual evoked potentials (P200 component of event-related potentials, $p = 0.02$), both the effects were small and, according to the authors, did not exceed the normal range during the sham exposures. A trend was observed for decreased performance of the Sternberg memory task following exposure to methanol ($p = 0.055$) although it is of borderline statistical significance. Consistent with this finding, subjects reported higher levels of fatigue and there was a trend toward decreased ability to concentrate and less vigor when exposed to methanol vapors compared to control conditions. According to the authors, these changes did not affect the subjects' ability to maintain vigilance or to respond quickly to stimuli.

Predisposing Conditions for Methanol Toxicity

Medical: Persons with skin, eye, respiratory or neurological conditions may be more sensitive to the adverse effects of methanol (Reprotext, 1999). There is a great range of individual response to the toxic effects of methanol, probably due to the variability in individual capacity to generate toxic metabolites (Bennet, 1953; NIOSH, 1976).

Chemical: Persons simultaneously exposed to formaldehyde or formic acid may be more sensitive. Those ingesting ethanol may be less sensitive to methanol toxicity (Reprotext, 1999).

V. Acute Toxicity to Laboratory Animals

With the exception of non-human primates, the signs of methanol toxicity in laboratory animals are quite different from the signs observed in humans (Gilger and Potts, 1955). The major effect of methanol in non-primates is CNS depression similar to that produced by other alcohols. Metabolic acidosis and ocular toxicity are not observed. The differences in toxicity are attributed to the ability of non-primates to more efficiently metabolize formate than humans and other primates (Tephly, 1991). The lethal oral dose of methanol in humans is estimated at approximately 1/3 and 1/9 the equivalent oral dose in monkeys and rats, respectively (Gilger and Potts, 1955).

In one poorly described study, 11 rhesus monkeys, 12 rabbits, and 46 rats were exposed by inhalation to methanol concentrations ranging from 1,000 ppm to 40,000 ppm (1,300 to 52,400 mg/m^3) for 1-18 hours/day for up to 41 hours (McCord, 1931). Of the species studied, monkeys were the most sensitive to the effects of methanol. Some animals (number and species unidentified) died after exposure to 1,000 ppm for at least 41 hours. Exposure at 40,000 ppm for 4 hours led to immediate death in all animals. A 1-hour exposure at this concentration led to "sickness in [all] animals within 2-3 days and eventually to death."

Twenty-four cynomolgus monkeys were exposed by inhalation to methanol vapor at concentrations up to 6,650 mg/m^3 (5,010 ppm) for 6 hours per day, 5 days per week for 4 weeks (Andrews *et al*., 1987). No deaths occurred and no treatment-related effects, including ocular damage, were observed.

Methanol has been shown to be a mild irritant to the eyes and skin of rabbits when applied topically (Rowe and McCollister, 1978).

Additionally, NIOSH (1976) cites studies by Flury and Wirth (1933) which reported a Lowest Lethal Concentration (LCLo) in cats of 33,082 ppm after a 6-hour exposure, and by Izmerov *et al*. (1982) which reported an LCLo in mice of 37,594 ppm after a 2-hour exposure.

VI. Reproductive or Developmental Toxicity

Exposure to methanol along with other solvents is believed to cause central nervous system birth defects in humans (Holmberg, 1979). However, because of mixed or inadequate exposure data, it is not considered a known human teratogen.

In two separate studies in male rats, inhalation exposure to methanol at concentrations ranging from 260 to 13,000 mg/m³ (200 to 9,900 ppm) for 6 to 8 hours per day for either 1 day or 1, 2, 4, or 6 weeks resulted in a significant reduction in circulating testosterone levels (Cameron *et al*., 1984; 1985). However, a dose-response relationship was not observed.

Pregnant rats were exposed by inhalation to methanol at concentrations ranging from 5,000 to 20,000 ppm (6,600 to 26,000 mg/m³) for 7 hours per day on days 1-19 of gestation, and days 7-15 for the highest dose group (Nelson *et al*., 1985). A dose-related decrease in fetal weight and increases in extra or rudimentary cervical ribs and in urinary and cardiovascular defects were observed. Exencephaly and encephalocele were observed in the 20,000 ppm dose group. The no observable adverse effect level (NOAEL) was 5,000 ppm.

Rogers *et al*., (1993) exposed pregnant mice to methanol vapors at concentrations ranging from 1,000 to 15,000 ppm (1,300 to 20,000 mg/m³) for 7 hours per day on days 6-15 of gestation. Increased embryonic and fetal death, including an increase in full-litter resorptions, was observed at 7,500 ppm (9,800 mg/m³) and higher. Significant increases in the incidence of exencephaly and cleft palate were observed at 5,000 ppm (6,600 mg/m³) and higher. A dose-related increase in the number of fetuses per litter with cervical ribs (usually small ossification sites lateral to the seventh cervical vertebra) was observed at 2,000 ppm (2,600 mg/m³) and above. The NOAEL was 1,000 ppm (1,300 mg/m³) methanol.

VII. Derivation of Acute Reference Exposure Level and Other Severity Levels (for a 1-hour exposure)

Reference Exposure Level (protective against mild adverse effects): 21 ppm (28,000 µg/m³)

Study	Cook *et al*., 1991
Study population	twelve healthy male volunteers
Exposure method	inhalation of 192 ppm (250 mg/m³)
Critical effects	subtle impairment in the performance of complicated tasks
LOAEL	not observed
NOAEL	192 ppm
Exposure duration	75 minutes
Extrapolated 1 hour concentration	214 ppm (192^2ppm * 1.25 h = C^2 * 1 h) (see Table 12 for information on “n”)
LOAEL uncertainty factor	1
Interspecies uncertainty factor	1
Intraspecies uncertainty factor	10
Cumulative uncertainty factor	10
Reference Exposure Level	21 ppm (28 mg/m³; 28,000 µg/m³)

The only exposure concentration tested, 250 mg/m³ (192 ppm), was considered a free-standing NOAEL for subtle neurologic effects. Reevaluation of the mild adverse effect level is recommended when a study of the neurobehavioral effects of methanol using a larger sample size becomes available.

Level Protective Against Severe Adverse Effects

A NOAEL of 1,000 ppm (1,300 mg/m³) for congenital malformations was observed in mice exposed for 7 hours/day on days 6 through 15 of gestation (Rogers *et al*., 1993). The investigators calculated maximum likelihood estimates (MLEs) and benchmark concentrations (BC, the lower 95% confidence limit of the MLEs) for both 1% and 5% added risks above background. The most sensitive developmental toxicity endpoint was an increase in the incidence of cervical ribs. The MLE_{01} and BC_{01} for cervical ribs were 302 ppm (393 mg/m³) and 58 ppm (75 mg/m³), respectively. The MLE_{05} and BC_{05} for this endpoint were 824 ppm (1,072 mg/m³) and 305 ppm (397 mg/m³), respectively.

The use of a quantitative dose-response model to estimate a benchmark dose has been described by Crump (1984). The recommended serious adverse effect level was calculated by adjusting the BC_{05} by an uncertainty factor (UF) of 30, 3 to account for interspecies variation since the BC approach accounts for some degree of variation and 10 to account for intraspecies extrapolation.

$$\text{7-hour level} = BC_{05}/(UF)$$

The 7-hour value was used as the basis for the level protective against severe adverse effects. The resulting level protective against severe adverse effects is 10 ppm (13 mg/m³), and is designed for a 7-hour exposure. Revision of this level, designed to protect against serious adverse effects is recommended when a primate reproductive study is available.

Level Protective Against Life-threatening Effects

No recommendation is made due to the limitations of the database.

NIOSH (1995) lists a (revised) IDLH for methyl alcohol of 6,000 ppm (7,860 mg/m³) based on the Izmerov *et al*. (1982) mouse acute inhalation toxicity data. NIOSH used the LC_{Lo} of 37,594 ppm from that study to calculate an adjusted 0.5-hour Lethal Concentration value of 60,150 ppm using a Correction Factor (CF) of 1.6, which was then divided by a safety factor of 10 to provide the IDLH value of 6,000 ppm (7,860 mg/m³). NIOSH asserts that this may be a conservative value due to the lack of relevant acute toxicity data for workers exposed to concentrations between 1,000 and 30,000 ppm. Additionally, NIOSH (1995) notes that the lethal human oral dose for methanol has been reported as being between 143 and 6,422 mg/kg, which they found equivalent to a 70-kg worker being exposed to about 7,000 to 225,000 ppm for 30 minutes, assuming a breathing rate of 50 liters per minute and 100% absorption. Assuming a 1-hour exposure and a breathing rate of 20 m³/day, the equivalent lethal inhalation exposure would be 3,864 - 124,200 ppm. Thus, the IDLH of 6,000 ppm may not be adequate protection for the general public.

VIII. References

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